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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,331	DEFREES ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *14-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/20/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-25 are pending.

2. Applicant's election of Group I (claims 1-13) in the reply filed on January 28, 2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 14-25 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 1-13, drawn to a compound having the formula: Ab-G-L-T, are being acted upon in this Office Action.

5. Claim 4 is objected to because the formula in claim 4 does not require the formula in claim 1. Claim 4 should be an independent claim.

6. The disclosure is objected to because of the following informalities (1) incorporation of subject matter into the patent application by reference to a hyperlink and/or other form of browser-executable code is/are considered to be an improper incorporation by reference. See MPEP 608.01(p), paragraph I regarding incorporation by reference. Therefore the embedded hyperlinks and/or other forms of browser-executable code disclosed on pages 71, line 10 of the instant specification are impermissible and require deletion. Where the hyperlinks and/or other forms of browser-executable codes are part of applicant's invention and are necessary to be included in the patent application in order to comply with the requirements of 35 U.S.C. 112, first paragraph, and applicant does not intend to have these hyperlinks be active links, then this objection will be withdrawn and the Office will disable these hyperlinks when preparing the patent text to be loaded onto the PTO web database. (2) the word "accylgalactosamine" at page 42, line 13 is misspelled. It would have been "acetylgalactosamine". (3) the double colon "::" at page 27, last line should be singular colon ":".

7. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter of claim 11. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification fails to provide proper antecedent basis for the formula recited in original claim 11. Amendment to the specification to include the formula as recited in claim 11 is required.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for antibody-toxin conjugate comprising a specific antibody such as the ones disclosed at page 38 that have an O-linked glycoxylation site for an attachment of one sugar selected from the group consisting of acetylgalactosamine, galactose, manose, GlcNAc, glucose, fucose or xylose to the hydroxyl side chain of a hydroxyamino acid on the serine or threonine for conjugation to toxin, **does not** reasonably provide enablement for an compound as set forth in claims 1-13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The claims encompass innumerous compound having various formulas such as the ones recited in claims 1, 4, 7, 8, 9, 10, 11, 12 and 13 wherein Ab is any antibody, G is any intact glycosyl linking group, L is any bond or any spacer moiety covalently joining G to T and T is any toxin that encompassed any chemotherapeutic agents. In some instances, the formulas are incomplete, see claims 4, 10, 11, 12, and 13.

Enablement is not commensurate in scope with how to make and use such compound for treating cancer by targeting any toxin or chemotherapeutic agents to the site of tumor.

According to MPEP 2164.01(a), factors considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

MPEP§ 2164.04 states that while the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. Accordingly, the factors most relevant to the instant rejection are addressed in detail below.

Claim 1 encompasses a genus of compound having the formula: Ab-G-L-T wherein Ab is any antibody, G is any intact glycosyl linking group, L is any bond or any spacer moiety covalently joining G to T and T is any toxin.

Claims 4-6 encompass any compound having the structure as set forth in claim 4 wherein L1 is any bond or any linker moiety, A is any amplifier moiety, or any dendrimer.

The specification discloses only the specific monoclonal antibodies that bind to CD20, CD3, TNF receptor, CD4, CEA, EGF or HER-2 receptor covalently linked to toxin via O-link glycosylation through a pacer such as polyethylene glycol, polylysine, or dendrimer PAMAM, sugar, see pages 19 and 38.

The specification does not disclose any *in vivo* working example of using any compound for treating cancer or any disease.

The state of the prior art; The relative skill of those in the art; and The predictability or unpredictability of the art: It is well known in the prior art that antibody depends on binding specificity associated with the structure i.e., six CDRs of immunoglobulin heavy and light chains of an antibody for targeting any toxin to cell or site of interest.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS (all six CDRs) in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79: 1979-1983, 1982; PTO 892). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding.

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the amino acid residues in the CDRs and the length of the antibody heavy chain complementarity determining region (CDR3) are critical for antigen specific binding site (see abstract, in particular). The length of the amino acid sequence that linked the CDRs of immunoglobulin light and heavy chains is important in maintaining their required conformation for binding and in vivo activity.

Further, the function of an antibody molecule is dependent on its three dimensional structure, which in turn is dependent on its primary amino acid sequence. Changing the amino acid sequence of an antibody may adversely affect its activity. Likewise, fragments of the antibody may not retain the appropriate three-dimensional structures necessary to foster binding activity. There are also critical framework residues which are also important in positioning the CDRs for interaction with antigen or which are involved in interactions between the heavy and

light chains. As such, an undue experimentation would be required to make and use the claimed compound as broadly as claimed.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

According to MPEP 2163, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Moba, B.V. v.Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed.Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and

knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated: "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional

characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention.

In the instant case, Claim 1 encompasses a genus of compound having the formula: Ab-G-L-T wherein Ab is any antibody, G is any intact glycosyl linking group, L is any bond or any spacer moiety covalently joining G to T and T is any toxin.

Claims 4-6 encompass any compound having the structure as set forth in claim 4 wherein L1 is any bond or any linker moiety, A is any amplifier moiety, or any dendrimer.

At the time of filing, the specification discloses only the specific monoclonal antibodies that bind to CD20, CD3, TNF receptor, CD4, CEA, EGF or HER-2 receptor covalently linked to toxin via O-glycosylation through a pacer such as polyethylene glycol, polylysine, or dendrimer PAMAM, sugar, see pages 19 and 38.

The specification does not describe other members of the antibody. The specification does not describe the binding specificity associated with the complete structure of any antibody for the claimed compound. The specification does not adequately describe the common structural attribute, i.e., intact glycosyl linking group other than the O-linked glycoxylation site for an attachment of one sugar selected from the group consisting of acetylgalactosamine, galactose, manose, GlcNAc, glucose, fucose or xylose.

The state of the art at the time of filing is such that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRS (all six CDRs) in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites.

Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 79: 1979-1983, 1982; PTO 892). Rudikoff et al teach

that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding.

Barrios et al (J Molecular Recognition 17: 332-338, 2004; PTO 892) teach the amino acid residues in the CDRs and the length of the antibody heavy chain complementarity determining region (CDR3) are critical for antigen specific binding site (see abstract, in particular). The length of the amino acid sequence that linked the CDRs of immunoglobulin light and heavy chains is important in maintaining their required conformation for binding and in vivo activity.

Further, the function of an antibody molecule is dependent on its three dimensional structure, which in turn is dependent on its primary amino acid sequence. Changing the amino acid sequence of an antibody may adversely affect its activity. Likewise, fragments of the antibody may not retain the appropriate three-dimensional structures necessary to foster binding activity. There are also critical framework residues which are also important in positioning the CDRs for interaction with antigen or which are involved in interactions between the heavy and light chains. Further, there is no single species of antibody-toxin conjugate has been disclosed to have targeting toxin to the site of interest. There is insufficient description of a common core structure that would allow one of skill in the art to practice the invention as claimed. The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of antibody covalently linked to a genus of intact glycosyl linking group or to a genus of spacer moiety to a genus of toxin as claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1103, Friday April 11, 2004.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 4 and 10-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Dependent claim 4, line 3, recites the phrase "L^1 is a bond or a linker moiety covalently joining S to A" (emphasis added) which renders the claim vague and indefinite. The metes and bounds of the claim are unclear because "S" has not been defined in dependent claim 4 or defined and recited in independent claim 1. Further, it is unclear if the wavy symbol at both end of the formula -L-A-L- is part of the claimed invention. For examination purposes, it is assumed that claim 4 recites that L^1 is a bond or a linker moiety covalently joining Ab to A, where Ab is an antibody and A is an amplifier moiety as defined in claim 1 and claim 4, respectively.

Claim 10 is indefinite because the metes and bounds of what would constitute "$\mathbf{X^3}$" cannot be determined since the formula in claim 10 does not define what "$\mathbf{X^3}$" is.

Claim 11 is indefinite because the structural formula does not contain Z^1 and Z^2 and suddenly lines 8-9 of claim 11 defines Z^1 is selected from the group consisting of O, S and NH; and Z^2 is selected from the group consisting of NH, and NH-(CH_2)q.

Claim 12 is indefinite because the terms "A", the superscript "T" and n in the formula are not defined.

Claim 13 is indefinite because the term "n" in claim 13 is not defined.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Leung et al (of record, J Immunology 154: 5919-5926, 1995; PTO 1449).

Leung et al (J Immunology 154: 5919-5926, 1995; PTO 1449) teaches a compound such as Ab -G-L-T wherein Ab is an antibody, G is an intact glycosyl linking group covalently joining Ab to L; L is a bond or a spacer moiety covalently joining G to T; and T is a cytotoxic agent doxorubicin or toxin (see page 5922, Figure 2, schematic representation of antibody hMN-14N or fragment thereof Fab2 having glycosyl linking group Asn-X-Ser/Thr covalently linked to H2N represent by chelator/drugs/toxin, in particular). Thus, the reference teachings anticipate the claimed invention.

16. Claims 1-9 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 7,125,843 (filed April 9, 2003 claimed earliest priority to Oct 10, 2001; PTO 892).

The '843 patent teaches a compound such as a conjugate comprising a peptide or an antibody targeting moiety such as anti-CD20 antibody (see col. 67, line 48-67, col. 143, line 34-41, col. 141, line 30-42, col. 339, line 1-13, in particular), an intact glycosyl linking group via a O-linked glycans originating from serine or threonine (see col. 12, line 33-35, col. 67, line 55-56, in particular) interposed between the antibody and the selected therapeutic moiety such as a toxin or cytotoxic agents, e.g. adriamycin, doxorubicin and taxol (see entire document col. 145, lines 66 through col. 146, line 5, col. 67, line 34-67, col. 67, line 18, col. 68, line 63, Table 2, col. 84, line 46-67, col. 166, line in particular). The reference linking moiety can be either a bond or a polyethylene glycol moiety or amplifier moiety (see col. 68, line 13-15, in particular). The reference PEG linker moiety can be linear or branched such as PEG comprises alkyl group (see col. 69, line 34-60, col. 75, line 66, col. 77, lines 7-8, in particular). The reference linker moiety can be alkyl, benzyl or aryl (see col. 77, line 23-32, in particular). The reference conjugate further comprises an amplifier moiety such as multiple PEG, polypropylene glycol (PPG) or alkylated amine (see col. 77, line 45-50, col. 147, line 46-52, in particular) or polyamine such as polylysine, polyaspartic acid, polyglutamate (see col. 75, line 20-21, col. 79, line 60-67, col. 166, lines 15-21, in particular). Those of skill in the art will appreciate that the conjugates between more than two peptides by, for example, by the use of a branched PEG, dendrimer, poly(amino acid), polysaccharide or the like (see col. 69, paragraphs 457-459, in particular). The PEG linker that includes two glycosyl groups is for purposes of clarity and should not be interpreted as limiting the identity of linker arms of use in this embodiment of the invention. Thus, a PEG

moiety is functionalized at a first terminus with a first glycosyl unit and at a second terminus with a second glycosyl unit. The first and second glycosyl units are preferably substrates for different transferases, allowing orthogonal attachment of the first and second peptides or antibodies to the first and second glycosyl units, respectively. In practice, the (glycosyl).sup.1-PEG-(glycosyl).sup.2 linker is contacted with the first peptide and a first transferase for which the first glycosyl unit is a substrate, thereby forming (peptide).sup.1-(glycosyl).sup.1-PEG-(glycosyl).sup.2. The first transferase and/or unreacted peptide or antibody is then optionally removed from the reaction mixture. The second peptide or antibody and a second transferase for which the second glycosyl unit is a substrate are added to the (peptide).sup.1-(glycosyl).sup.1-PEG-(glycosyl).sup.2 conjugate, forming (peptide).sup.1-(glycosyl).sup.1-PEG-(glycosyl).sup.2-(peptide).sup.2. Claim 10 is included in this rejection because the reference antibody is lined to a sugar via O-link to polymer such as polyethylene glycol that includes one or more (CH2)m from 0 to 20 and Z is a bond or OCH2CH2 (see col.75, lines 55 through col. 77, lines 61, in particular) and a cleavable linker groups (see col. 173, lines 4-25, in particular). Thus, the reference teachings anticipate the claimed invention.

17. Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi et al (Eur J Nuclear Med 27(9): 1334-1339, Sept 2000; PTO 892).

For examination purpose, claim 4 is interpreted to be antibody linked to an amplifier moiety dendrimer and any therapeutic via a bond since the term "S" and wavy lines are not defined. Further, the formula in claim 1 does not contain "A", the amplifier moiety.

Kobayashi et al teach a compound such as a conjugate such as 153Gd or 111-In-OST7-G4-(1B4M)43 comprising radioisotope covalently linked to an antibody such as OST7 (IgG1) that linked through a SH bond to an amplifier moiety such as PAMAM dendrimer (G4) where the G4 is linked to (1B4M)43 complex (see page page1334. col. 1, in particular). The reference L1 and L2 are bonds such as SH bond (see page 1335, col. 2, Fig 2, in particular). Thus, the reference teachings anticipate the claimed invention.

18. Claims 1-4, 7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 6,743,896 (filed Sept 20, 2001 claimed earliest priority to June 23, 1997; PTO 892).

The '896 patent teaches a compound comprising a single chain antibody such as SCA, an intact glysosyl linking group such as N-linked glycosylated covalently attached to a toxin via a

bond (see col. 29, line 32-33, col. 30, line 39-60, col. 29, line 20-23, claims 1, 10-11 of the '896 patent, in particular). The reference liker moiety is a member of the alkyl group (see coll. 27, line 30-36, in particular). The spacer moiety may be a heteroalkyl, alkoxyl, alky moieties (see col. 28, line 15-20, in particular). The '896 patent further polyethylene glycol or activated polyalkylene oxide (PAO) as a linker moiety attached to the carbohydrate (see col. 28, line 65-col. 42, line 39-40, in particular). The reference polyethylene glycol (PEG) can be straight chain (see col. 22, line 25-58, in particular) or branched (see col. 28, line 24-45, in particular). Thus, the reference teachings anticipate the claimed invention.

19. Claims 10, 11, 12 and 13 are unsearchable.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

22. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
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